Review article

Is asthma increasing?

MICHAEL L. BURR

From the MRC Epidemiology Unit (South Wales), 4 Richmond Road, Cardiff

Asthma mortality is again causing concern. An epidemic of deaths occurred in several countries among young people during the 1960s. In Britain, asthma mortality became higher than it had been at any time in the previous hundred years, throughout which it had been fairly stable.¹ The epidemic subsided, and by 1974 the death rate had returned to its previous level. In view of the advances in treatment and management since the 1950s it might have been expected that mortality would now be well below pre-epidemic rates. But, in fact, the death rate during the later 1970s remained at about the same level as before. Currently it is showing an alarming tendency to drift upwards again (fig 1). What is going wrong?

International comparisons reveal some striking differences in the pattern of asthma mortality. Caution is obviously required in comparing data from different countries which may use different diagnostic criteria. Death rates among children and young adults are least liable to diagnostic confusion, however, since in this age group the mortality from acute and chronic bronchitis is very low. It appears to be a fact that the epidemic in the 1960s occurred in some countries (eg, Britain, Ireland, Australia, New Zealand and Norway) but not in others (eg, the United States, Canada, Belgium, and West Germany).² It was noticed that the countries affected had licensed the use of pressurised aerosols containing high concentrations of sympathomimetic amines, and this led to the suggestion that over use of these drugs had caused the excess mortality.³ This explanation has since been challenged, however,^{4,5} and the issue continues to be debated.

The present rise in mortality is not occurring in all countries. New Zealand seems to have experienced a particularly sharp rise since 1975, and death rates there are now even higher than they were during the previous epidemic.⁶ American and Canadian rates have been remarkably low and stable for many years,⁶ although among children under 14 years of age there has been a recent tendency for asthma deaths to rise in the United States from 1.0 per million in 1977 to 2.2 per million in 1983.⁷ West Germany, which was also

Fig 1 Deaths from asthma in England and Wales among persons aged 5 to 24 years.

unaffected by the previous epidemic, has recently shown an upward trend.⁶ It is difficult to avoid the impression of a general worsening of mortality, which affects some countries more than others.

Hospital admissions for childhood asthma have risen steeply during recent years. Figure 2 shows that the rates for all hospitals in Wales increased by more than fourfold from 1968 to 1984. The rates refer to

Fig 2 Patients aged 5 to 14 years discharged from Welsh hospitals with diagnosis of asthma.

numbers of Welsh children aged 5 to 14 years discharged from hospital with a diagnosis of asthma, expressed per thousand living in Wales. Thus a child admitted twice in one year contributes two admissions to that year's figures. In the South West Thames Region the number of different patients aged 5 to 14 years admitted for asthma increased by 130% between 1970 and 1978, while the number of spells rose by 167%, indicating an increase in readmissions.⁸ There seems to have been a disproportionately large rise in the number of self-referrals to hospital; admissions for bronchitis are relatively uncommon and have not changed substantially during this period,^{8,9} so that the rise in asthma admissions is not attributable to a change in diagnostic fashion. Much of the rise in hospitalisation has resulted from an "open-door" policy whereby self-referral is encouraged in the belief that it saves lives.¹⁰ To some extent it probably reflects a greater readiness of general practitioners to refer asthmatic patients to hospital, their increased caution no doubt arising from awareness of the epidemic of the 1960s. But the possibility remains that some other changes contribute both to this phenomenal increase and to the rising death rate.

Several hypotheses have been put forward in order to explain the rise in asthma mortality. These hypotheses, and others that may yet be suggested, can be classified as follows.

1 *Artefact of coding.* The simplest explanation of the apparent rise in mortality is that it is due to a change in the coding of cause of death on the death certificate. The International Classification of Diseases (ICD) has

been revised twice during the period under consideration, together with the rules for coding causes of death. While the seventh revision was in operation, deaths from asthma with mention of acute bronchitis were attributed to bronchitis unless the asthma was stated to be allergic. The eighth revision (introduced in 1968) led to the exclusion of asthma deaths with mention of bronchitis (acute, chronic or unspecified), bronchiolitis or emphysema, death being attributed to the other condition. The effect was therefore to reduce slightly the apparent number of asthma deaths. A bridge-coding exercise suggested that this produced a 4% fall among persons under 45 years of age. The introduction of the ninth revision in 1979 had a greater effect in the opposite direction, all the above exclusions being removed, so that all deaths certified as due to asthma were attributed to that disease irrespective of other conditions mentioned on the certificate. Again, a sample was bridge-coded, and the results suggested that the change produced a 9% rise in deaths assigned to asthma among persons under 45 years of age.¹¹ A further modification of the coding rules occurred in 1984, which allowed a "major disease" mentioned in Part II of the death certificate to take precedence over certain conditions (including bronchopneumonia, unspecified pneumonia, and cardiac failure) in Part I, where the underlying cause of death is normally entered. This change is likely to have increased the number of deaths assigned to asthma by about 4% for all persons under 75 years of age.¹² All these changes are unlikely to have more than a marginal effect, however, and two detailed statistical analyses of recent trends suggest that changes in coding practice are not the explanation of the rise in asthma mortality since 1974.^{13,14}

2 *Artefact of diagnosis.* Another kind of artefact arises from the possibility that clinical criteria for diagnosing asthma may have changed over time. This suggestion is far more difficult to investigate than an artefact of coding, since it is obviously impossible to decide with certainty how fatal events of ten years ago would be described if they happened now. As part of a confidential enquiry into asthma deaths, 153 death certificates of persons who died in 1979 aged 15 to 64 years were examined by a panel who had access to detailed clinical information about the patients.¹⁵ There appeared to be a net overestimate of 13% in the diagnosis of asthma in this sample, the accuracy being greatest in the youngest age group. It therefore seemed unlikely that inaccurate diagnosis made much contribution to the apparently high asthma mortality in young people. Only death certificates which mentioned the word "asthma" were examined, however, so there was no information about false negatives where asthma was totally unrecognised. A

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validation study in New Zealand (where asthma mortality is now exceptionally high) undertook a search for false negatives among a wider range of death certificates: only one possible false negative and no false positives were detected out of 76 apparent non asthmatics and 18 apparent asthmatics.⁶ The accuracy of death certification of asthma seems to be similar in New Zealand and England.¹⁶ Of course, we do not know whether accuracy in diagnosis has improved during recent years. It is noteworthy, however, that overall respiratory mortality in young people has been falling steadily in many countries.⁶ For example, among persons aged 5 to 24 years, there were twice as many asthma deaths in 1981 as in 1976 (129 compared with 65) but only three-quarters as many deaths from all respiratory causes (364 compared with 484) in England and Wales.^{17 18} It is difficult to envisage the variation in accuracy of diagnosis over this period that would have accounted for these changes.

3 Failure in management. A more worrying explanation is a failure in management of asthma, whether the chronic condition or the acute attack. Many physicians now consider that this was the cause of the epidemic in the 1960s; the high-pressure sympathomimetic aerosols induced a false sense of security among patients and doctors so that severe asthma was not perceived as a dangerous emergency when it occurred. As soon as the epidemic was recognised it subsided, since doctors, patients, and relatives at once became aware of the dangers of postponing an admission to hospital during an acute attack. The fact that the epidemic was at first attributed to a toxic effect of the aerosols reinforced the general awareness of a need for greater caution in treating the acute condition. Confidential investigations of fatal attacks have revealed serious defects in management, patients, relatives, and doctors failing to recognise the seriousness of an attack.^{19 20} It seems to be undeniable that many asthma deaths are preventable. The higher mortality among blacks compared with whites in the United States has been attributed to inferior medical care, and the relatively high British mortality to the low per capita expenditure on health compared to other countries.²¹ This explanation does not account for the fact that the British and Australian death rates are similar despite the fact that health expenditure in Australia is twice that in Britain. A more fundamental issue is that the "failure in management" hypothesis assumes that the quality of care has recently deteriorated simultaneously in several western countries. No doubt some deaths are – alas – due to the carelessness of patients, or doctors, or both. But is it likely that everyone is now more careless than they were in 1976 and 1959, when the death rates were

lower despite a more limited therapeutic armamentarium? And can we conceivably reconcile the notions of increasing carelessness (raising the death rate) and simultaneously increasing caution (quadrupling the hospital admission rate)? It is difficult to explain this combination of trends simply in terms of a failure to apply existing knowledge.

4 Consequence of treatment. An even more worrying possibility is that deaths are occurring because of, not in spite of, the treatment being given. This explanation was at first put forward to account for the epidemic in the 1960s. It was suggested that high concentrations of sympathomimetic aerosols may have caused death, either by means of cardiotoxic effect of the drugs or propellants, or by causing bronchodilatation without increased oxygenation, or by precipitating rebound broncho constriction on stopping the treatment.^{3 22 23} This explanation was largely abandoned for various reasons. Post mortem examinations showed that victims had asthma of sufficient severity to account for their deaths without the need to invoke a cardiotoxic effect of treatment.^{4 22} Asthma mortality rose and fell in Australia during a period of progressively rising aerosol sales.⁵ The international data showed other inconsistencies in relation to aerosols, notably in the Netherlands, Scandinavia, and Japan.²⁴ Overusage of bronchodilators did not seem to produce toxic effects or high blood levels of propellants.^{25 26}

More recently, however, it has been suggested that a change in prescribing habits may have contributed to the current epidemic of deaths in New Zealand, where there has been a considerable increase in the use of sustained release oral theophylline preparations. It has been postulated that theophylline and inhaled β -2 agonists have an additive toxic effect which at high doses may induce cardiac arrest.²⁷ Other recent changes of possible relevance include the advent of inhaled steroids and home nebulisers.²⁸

There is no doubt that drug sales of sympathomimetic aerosols, steroid aerosols, and theophylline have increased considerably in New Zealand and to a greater extent than in Australia or the United Kingdom. But the New Zealand rise in mortality occurred about three years before the sharp rise in drug sales, so the changes in prescribing are more likely to have been a response to a change in the disease rather than a cause of it.²⁹ Furthermore, a detailed investigation found no evidence of bronchodilator drug toxicity, cardiac arrhythmias, excess dosage or high blood theophylline levels in victims of asthma in New Zealand.¹⁶ The use of home nebulisers did not seem to be especially implicated; some over-reliance on nebulisers had occurred, but this accounted for at most 8% of deaths and did not explain the high mortality in New Zealand.³⁰

5 *Change in disease.* The final and most mysterious possibility to be considered is that there has been a change in the natural history of the disease itself. Its prevalence, or its severity, or both, may be increasing for reasons that are quite unknown. Obviously this would contribute to the rising hospital admission rate as well as the rising mortality.

In considering this explanation we would naturally ask whether the prevalence of asthma appears to be increasing. It is indeed tantalising to find that the evidence does not allow a definite answer. Asthma is notoriously difficult to define, so that we cannot be sure whether past and present surveys are defining the disease in the same way. Often the investigators have simply asked subjects whether they have had asthma. Some surveys have included untreated asthma and ex-asthma while others have not. Studies of bronchial provocation tests have not all been carried out in the same way, and in any case it is not clear how closely the results of such tests correspond with the spontaneous disease.

Notwithstanding these uncertainties, there is some evidence to support the idea that underlying changes in natural history are occurring. The detailed studies of asthma deaths in England and New Zealand suggested that "non-preventable" death is commoner in New Zealand, so that the disease may be more severe there.¹⁶ Another survey found the prevalence of asthma to be 11% and 25% respectively among Tokelauan children living in Tokelau and in New Zealand.³¹ The New Zealand Tokelauans also had a higher prevalence of rhinitis and eczema, the latter disease occurring in 8.5% (99 out of 1160) compared with only 0.1% (1 out of 706) in Tokelau. These findings suggest that some environmental factor operates in New Zealand to produce a high prevalence of asthma there. Similarly, a survey in South Africa showed that exercise-induced asthma was far commoner among urban compared with rural children of the same genetic stock (Xhosa) – 3.2% and 0.1% respectively.³²

There is some evidence to suggest that allergic disease is becoming more common in Britain. Smith³² has published data showing a rise in the prevalence of reported asthma and wheezing among Birmingham schoolchildren, although it is not clear from his data whether the groups were entirely comparable in age. Eaton³³ found a rise in the frequency of allergy in a general practice over a five-year period. Morbidity surveys in general practices throughout England and Wales show a rise in the age-standardised prevalence of asthma from 11.6 to 20.5 men and from 8.8 to 15.9 women per 1000 population between 1970-1 and 1981-2. During the same period the prevalence of hay fever nearly doubled, becoming almost four times higher than the rate in 1955-6.³⁴ Physicians in Western

Europe, Eastern Europe, the United States, and Japan believe that asthma and other allergic diseases are becoming more common.³⁵ A comparison of several successive cohorts and other surveys shows that the reported prevalence of eczema has risen steadily during the last 40 years or so.³⁶ Hay fever and eczema are no doubt subject to as many diagnostic inaccuracies as asthma, but it is remarkable that the prevalence of related diseases should appear to be rising.

If asthma really is becoming more common or severe, various mechanisms may be involved. It may be that atopic persons are becoming exposed to more allergens and other factors which provoke bronchoconstriction than was previously the case. If this is so it should be possible to correlate changes in the disease with changes in exposure to these factors, and also (in principle at least) to reverse the current trend by reducing the degree of exposure. Fluctuations in numbers of airborne hyaline ascospores have been suggested as a potential factor,³⁷ but it seems strange that the rise in mortality should be occurring in countries so climatically different and far apart. Colourants and additives in food have also been suspected, but tests of withdrawal and challenge do not confirm these suspicions.^{38 39}

It is, however, possible that the disease is changing for some reason other than increased exposure to factors with an immediate effect. Perhaps some environmental changes are increasing the risk of becoming allergic or are potentiating the effects of allergens to which people have always been exposed. If this should be so, it will be extremely difficult to detect the cause of the present upward drift, particularly if the effect is long-term. The apparent rise in prevalence of hay fever and eczema does suggest that some cohort effect may be at work. We need some plausible hypotheses from the immunologists. Meanwhile we can at least attempt to determine what is really happening to the prevalence and severity of asthma. It would be a start to conduct surveys in different areas which could be repeated at intervals to show what is going on, and even better, to reproduce past surveys using exactly the same methodology as before. We do not want to find, ten years hence, that the death rate has continued to rise while we still do not know what has happened to the prevalence.

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Correspondence and requests for reprints: Pr J Faivre, Faculté de Médecine, 7 Boulevard Jeanne d'Arc, 21033 Dijon, France.

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Correction

In the paper by Michael L Burr (1987, **41**, 185-9) the first of the two references 32 in the text should relate to the following:

Weinberg EG, van Niekerk CH, Shore SC, Heese H de V, van Schalkwyk DJ. Prevalence of asthma. *Lancet* 1977; ii: 500.